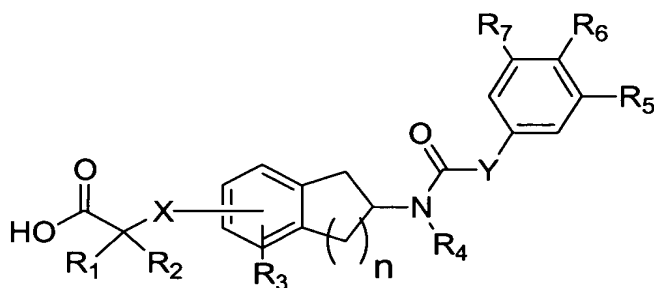


CLAIMS

1. A compound of Formula I

5



Formula I

or a pharmaceutically acceptable salt, C₁₋₆ ester or C₁₋₆ amide thereof, wherein

10

each of R₁ and R₂ is independently H, C₁₋₆ alkyl, (CH₂)_mNR_aR_b, (CH₂)_mOR₈, (CH₂)_mNH(CO)R₈, or (CH₂)_mCO₂R₈, where each of R_a, R_b, and R₈ is independently H or C₁₋₆ alkyl, or R₁ and R₂ taken together with the carbon atom to which they are attached are a C₃₋₇ cycloalkyl;

15

m is between 1 and 6;

n is 1 or 2;

X is O or S; wherein X is at the 5 or 6 position when n is 1; and wherein X is at the 6 or 7 position when n is 2;

20

R₃ is H, phenyl, C₁₋₃ alkoxy, C₁₋₃ alkylthio, halo, cyano, C₁₋₆ alkyl, nitro, NR₉R₁₀, NHCOR₁₀, CONHR₁₀; and COOR₁₀; and R₃ is ortho or meta to X;

25

R₄ is H or -(C₁₋₅ alkylene)R₁₅, where R₁₅ is H, C₁₋₇ alkyl, [di(C₁₋₂ alkyl)amino](C₁₋₆ alkylene), (C₁₋₃ alkoxyacyl)(C₁₋₆ alkylene), C₁₋₆ alkoxy, C₃₋₇ alkenyl, or C₃₋₈ alkynyl, wherein R₄ has no more than 9 carbon atoms; R₄ can

also be $-(C_{1-5} \text{ alkylene})R_{15}$ wherein R_{15} is C_{3-6} cycloalkyl, phenyl, phenyl-O-, phenyl-S-, or a 5-6 membered heterocyclyl with between 1 and 2 heteroatoms selected from N, O, and S;

5 Y is NH, NH-CH₂, and O;

each of R_5 and R_7 is independently selected from H, C_{1-6} alkyl, halo, cyano, nitro, COR₁₁, COOR₁₁, C_{1-4} alkoxy, C_{1-4} alkylthio, hydroxy, phenyl, NR₁₁R₁₂ and 5-6 membered heterocyclyl with between 1 and 2 heteroatoms selected
10 from N, O, and S;

R_6 is selected from C_{1-6} alkyl, halo, cyano, nitro, COR₁₃, COOR₁₃, C_{1-4} alkoxy, C_{1-4} alkylthio, hydroxy, phenyl, NR₁₃R₁₄ and 5-6 membered heterocyclyl with between 1 and 2 heteroatoms selected from N, O, and S;
15

in addition, either R_5 and R_6 or R_6 and R_7 may be taken together to be a bivalent moiety, saturated or unsaturated, selected from $-(CH_2)_3-$, $-(CH_2)_4-$, and $(CH_{1-2})_pN(CH_{1-2})_q$,

20 p is 0-2 and q is 1-3, where the sum (p + q) is at least 2;

each of R_9 and R_{10} is independently C_{1-6} alkyl;

each of R_{11} , R_{12} , R_{13} and R_{14} is independently H or C_{1-6} alkyl;

25 wherein each of the above hydrocarbyl and heterocarbyl moieties may be substituted with between 1 and 3 substituents independently selected from F, Cl, Br, I, amino, methyl, ethyl, hydroxy, nitro, cyano, and methoxy.

2. A compound of claim 1, wherein one of R_1 and R_2 is methyl or ethyl.
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3. A compound of claim 2, wherein each of R_1 and R_2 is methyl.

4. A compound of claim 1, wherein R_1 and R_2 taken together are cyclobutyl or cyclopentyl.
- 5 5. A compound of claim 1, wherein R_3 is H.
6. A compound of claim 1, wherein R_3 is C_{1-3} alkoxy, C_{1-3} alkylthio, halo, cyano, C_{1-6} alkyl, nitro, NR_9R_{10} , $NHCOR_{10}$, $CONHR_{10}$; or $COOR_{10}$.
- 10 7. A compound of claim 1, wherein R_4 is H or C_{2-7} alkyl.
8. A compound of claim 7, wherein R_4 is H or C_{2-5} alkyl.
9. A compound of claim 8, wherein R_4 is ethyl.
- 15 10. A compound of claim 8, wherein R_4 is H.
11. A compound of claim 1, wherein n is 1.
- 20 12. A compound of claim 1, wherein n is 2.
13. A compound of claim 1, wherein Y is $NH-CH_2$.
14. A compound of claim 1, wherein Y is NH .
- 25 15. A compound of claim 1, wherein X is S.
16. A compound of claim 1, wherein X is O.
- 30 17. A compound of claim 1, wherein at least one of R_5 and R_7 is H.

18. A compound of claim 17, wherein R₆ is C₁₋₄ alkyl, halomethoxy, halomethylthio, or di(C₁₋₃ alkyl)amino.

19. A compound of claim 18, wherein R₆ is trifluoromethoxy, difluoromethoxy, trifluoromethyl, trifluoromethylthio, t-butyl, isopropyl, or dimethylamino.

20. A compound of claim 3, wherein R₃ is H, R₄ is C₂₋₇ alkyl, and Y is NH.

21. A compound of claim 20, wherein X is S.

22. A compound of claim 20, wherein n is 1.

23. A compound of claim 20, wherein n is 2.

24. A compound of claim 20, wherein R₄ is C₂₋₅ alkyl.

25. A compound of claim 24, wherein R₄ is ethyl.

26. A compound of claim 20, wherein R₆ is trifluoromethoxy, difluoromethoxy, trifluoromethyl, trifluoromethylthio, t-butyl, isopropyl, or dimethylamino.

27. A compound of claim 1, wherein each of R₁ and R₂ is independently H, C₁₋₆ alkyl, (CH₂)_mNR_aR_b, or (CH₂)_mOR₈, where each of R_a, R_b, and R₈ is independently H or C₁₋₆ alkyl;

m is between 1 and 6;

n is 1 or 2;

X is O or S; wherein X is at the 5 or 6 position when n is 1; and wherein X is at the 6 or 7 position when n is 2;

R₃ is H, phenyl, C₁₋₃ alkoxy, C₁₋₃ alkylthio, halo, C₁₋₆ alkyl, or NR₉R₁₀, and R₃ is ortho or meta to X;

R₄ is H or -(C₁₋₅ alkylene)R₁₅, where R₁₅ is H, C₁₋₇ alkyl, [di(C₁₋₂ alkyl)amino](C₁₋₆ alkylene), (C₁₋₃ alkoxyacyl)(C₁₋₆ alkylene), C₁₋₆ alkoxy, or C₃₋₇ alkenyl, wherein R₄ has no more than 9 carbon atoms;

R₄ can also be -(C₁₋₅ alkylene)R₁₅ wherein R₁₅ is C₃₋₆ cycloalkyl, phenyl, phenyl-O-, phenyl-S-, or a 5-6 membered heterocyclyl with between 1 and 2 heteroatoms selected from N, O, and S;

Y is NH or NHCH₂;

each of R₅ and R₇ is independently selected from H, C₁₋₆ alkyl, halo, COR₁₁, COOR₁₁, C₁₋₄ alkoxy, C₁₋₄ alkylthio, hydroxy, and NR₁₁R₁₂;

R₆ is selected from C₁₋₆ alkyl, halo, COR₁₃, COOR₁₃, C₁₋₄ alkoxy, C₁₋₄ alkylthio, phenyl, NR₁₃R₁₄ and 5-6 membered heterocyclyl with between 1 and 2 heteroatoms selected from N, O, and S;

each of R₉ and R₁₀ is independently C₁₋₆ alkyl;

each of R₁₁, R₁₂, R₁₃ and R₁₄ is independently H or C₁₋₆ alkyl;

wherein each of the above hydrocarbyl and heterocarbyl moieties may be substituted with between 1 and 3 substituents independently selected from F, Cl, amino, methyl, ethyl, hydroxy, and methoxy.

28. A compound of claim 1, selected from:

2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid;

2-{2-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]indan-5-ylsulfanyl}-2-methylpropionic acid;

2-{2-[1-Ethyl-3-(4-trifluoromethylsulfanylphenyl)ureido]indan-5-ylsulfanyl}-2-methylpropionic acid;

2-Methyl-2-{2-[1-pentyl-3-(4-trifluoromethylsulfanylphenyl)ureido]indan-5-ylsulfanyl}propionic acid;

5 2-{2-[1-Ethyl-3-(4-isopropylphenyl)ureido]indan-5-ylsulfanyl}-2-methylpropionic acid;

2-Methyl-2-{2-[1-pentyl-3-(4-trifluoromethoxyphenyl)ureido]indan-5-ylsulfanyl}-2-methylpropionic acid;

10 2-{2-[3-(4-Dimethylaminophenyl)-1-ethylureido]indan-5-ylsulfanyl}-2-methylpropionic acid;

2-Methyl-2-{2-[1-(3-methylbutyl)-3-(4-trifluoromethoxyphenyl)ureido]indan-5-ylsulfanyl}-2-methylpropionic acid;

2-{2-[3-(4-Isopropylphenyl)-1-(3-methylbutyl)ureido]indan-5-ylsulfanyl}-2-methylpropionic acid;

15 2-Methyl-2-{2-[1-pent-4-enyl-3-(4-trifluoromethoxyphenyl)ureido]indan-5-ylsulfanyl}propionic acid;

2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-3-methoxy-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid;

20 2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-3-fluoro-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid;

2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-3-chloro-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid;

2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-3-bromo-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid;

25 2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-3-methyl-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid; and

2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-3-trifluoromethoxy-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid.

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29. A compound of claim 1, selected from

2-Methyl-2-{2-[1-hexyl-3-(4-trifluoromethylsulfanylphenyl)ureido]indan-5-ylsulfanyl}propionic acid ;

2-{2-[3-(4-Dimethylaminophenyl)-1-pentylureido]indan-5-ylsulfanyl}-2-methylpropionic acid;

5 2-Methyl-2-{2-[3-(4-trifluoromethoxyphenyl)ureido]indan-5-ylsulfanyl}propionic acid;

2-Methyl-2-{2-[1-propyl-3-(4-trifluoromethoxyphenyl)ureido]indan-5-ylsulfanyl}propionic acid;

10 2-Methyl-2-{2-[1-butyl-3-(4-trifluoromethylsulfanylphenyl)ureido]indan-5-ylsulfanyl}propionic acid;

2-{2-[3-(4-Isopropylphenyl)-1-(3-pentyl)ureido]indan-5-ylsulfanyl}-2-methylpropionic acid;

2-{2-[3-(4-*tert*-Butylphenyl)-1-(3-pentyl)ureido]indan-5-ylsulfanyl}-2-methylpropionic acid;

15 2-[2-(3-(Biphenyl-4-yl-1-pentylureido)indan-5-ylsulfanyl)-2-methylpropionic acid;

2-{2-[3-(4-Isopropylphenyl)-1-(3-hexyl)ureido]indan-5-ylsulfanyl}-2-methylpropionic acid;

20 2-Methyl-2-{2-[1-butyl-3-(4-trifluoromethoxyphenyl)ureido]indan-5-ylsulfanyl}propionic acid;

2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-3-methoxy-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid;

2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-3-fluoro-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid;

25 2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-3-chloro-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid;

2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-3-bromo-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid;

30 2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-3-methyl-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid; and

2-Methyl-2-{2-[1-hexyl-3-(4-trifluoromethoxyphenyl)ureido]indan-5-ylsulfanyl}propionic acid.

30. A compound of claim 1, selected from:

- 5 2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid;
- 2-{6-[3-(4-Trifluoromethoxyphenyl)ureido]-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid;
- 2-{2-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]indan-5-ylsulfanyl}-2-
- 10 methylpropionic acid;
- 2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-3-fluoro-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid;
- 2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-3-methyl-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid;
- 15 2-{2-[1-Ethyl-3-(4-trifluoromethylsulfanylphenyl)ureido]indan-5-ylsulfanyl}-2-methylpropionic acid; and
- 2-Methyl-2-{2-[1-propyl-3-(4-trifluoromethoxyphenyl)ureido]indan-5-ylsulfanyl}propionic acid.

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31. A compound of claim 1, selected from:

- 2-{2-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]indan-5-ylsulfanyl}-2-methylpropionic acid;
- 2-{2-[1-Ethyl-3-(4-trifluoromethylsulfanylphenyl)ureido]indan-5-ylsulfanyl}-2-
- 25 methylpropionic acid;
- 2-Methyl-2-{2-[1-propyl-3-(4-trifluoromethoxyphenyl)ureido]indan-5-ylsulfanyl}propionic acid; and
- 2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-3-fluoro-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid.

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32. A pharmaceutical composition, comprising a compound of claim 1, 20, 27, 28, 30, or 31.

5 33. A method for treating or inhibiting the progression of a PPAR-alpha mediated disease, said method comprising administering to a patient in need of treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1, 20, 27, 28 or 31, wherein said PPAR-alpha mediated disease is selected from impaired glucose tolerance, hyperinsulinemia, hyperglycemia, insulin resistance, and early, intermediate or late Type II
10 diabetes (NIDDM), and complications thereof.

34. A method of claim 33, wherein said complication is selected from retinopathy, nephropathy, and neuropathy.

15 35. A method of claim 33, wherein said PPAR-alpha mediated disease is selected from impaired glucose tolerance, insulin resistance, hyperglycemia, hyperinsulinemia, and early Type II diabetes, and complications thereof.

20 36. A method of claim 33, wherein said PPAR-alpha mediated disease is selected from intermediate or late Type II diabetes, and complications thereof.

25 37. A method of claim 33, wherein said compound of claim 1, 20, 27, 28, or 31 is a first anti-diabetic agent, and wherein said method further comprises the step of administering to the patient a jointly-effective amount of a second anti-diabetic agent.

30 38. A method of claim 37, wherein said second anti-diabetic agent is selected from PPAR alpha and PPAR gamma modulating agents.

39. A method of claim 37, wherein said second anti-diabetic agent is insulin.

40. A method of claim 33, further comprising the step of administering a jointly-effective amount of a third pharmaceutically active agent.

5 41. A method of claim 40, wherein said third pharmaceutically active agent is selected from an anti-diabetic agent, a lipid lowering agent, and a blood-pressure lowering agent.

10 42. A method both for treating or inhibiting the progression of a PPAR-alpha mediated disease and for treating or inhibiting the progression of dyslipidemia, said method comprising administering to a patient in need of treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1, 20, 27, 28 or 31, wherein said PPAR-alpha mediated disease is selected from impaired glucose tolerance, hyperinsulinemia,
15 insulin resistance, and early, intermediate or late Type II diabetes (NIDDM), and complications thereof.

43. A method of claim 42, wherein said composition consists essentially of a compound of claim 1, 20, 27, 28, or 31.

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